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09/719,067	08/16/2001	David B. Weiner	UPAP0025-100	4038

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EXAMINER	
KELLY, ROBERT M	

ART UNIT	PAPER NUMBER
1633	

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12/24/2008	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	09/719,067	WEINER ET AL.	
	Examiner	Art Unit	
	ROBERT M. KELLY	1633	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *14 October 2008*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *9,15,16,40-46 and 48* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *9,15,16,40-46 and 48* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Applicant's amendment and response of 10/14/08 are entered.

Claims 9 and 40 are amended.

Claims 34 and 47 are cancelled.

Claims 9, 15, 16, 40-46, and 48 are presently pending and considered.

Claim Status, Cancelled Claims

In light of the cancellation of Claims 34 and 47, all rejections and/or objections to such claims are rendered moot, and thus, are withdrawn.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 9, 15, 16, 40-46, and 48 are newly rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention, as necessitated by amendment.

Claim 9 recites the limitation "said free DNA". There is insufficient antecedent basis for this limitation in the claim.

Claims 15 and 16 are rejected for depending from a rejected base claim and not overcoming the lack of clarity therein.

Claim 40 recites the limitation "said DNA molecule". There is insufficient antecedent basis for this limitation in the claim.

Claim 41, 43-46, and 48 recites the limitation "said DNA molecule" in Claim 40. There is insufficient antecedent basis for this limitation in the claim. To wit, there is no antecedent basis in the base claim, so there is none when it is referred to in the dependent claims.

Claims 41, 42-46, and 48 are, or are also, rejected for depending from a rejected base claim, and not overcoming the lack of clarity in the base claim.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 9, 15-16, and 40-46, and 48 remain rejected, under 35 U.S.C. 103(a) as being unpatentable over US PAT APP NO 2004/0063652 to Jolly, Kataoka, et al. (1997) J. Biol. Chem., 272(29): 18209-15, US PAT NO 5,783,567 to Hedley, et al., Samlowski, et al. (1988) Regional Immunology, 1(1): 41-55, US PAT NO 5,763,416 to Bonadio, et al, for reasons of record as necessitated by the amendments.

Jolly teaches the use of plasmids (e.g., paragraph 0037) to effect the transformation of macrophage cells, to effect killing (e.g., paragraphs 0067-71) and for general secretion of proteins that block pathogenic interactions local to the cell (paragraph 0155), which requires secretion signals.

Kataoka teaches the human CD156 gene, and its promoter sequence as specific for macrophage expression, as well as the structure of such promoters (p. 18215).

Hedley teaches the transformation of macrophages of the draining lymph nodes by subcutaneous injection (e.g., col. 8, paragraph 3), and Samlowski teaches that macrophages were known to drain to the lymph nodes local to the site of injection (e.g., ABSTRACT), hence, macrophages drain locally and not distantly.

Bonadio teaches that the SV40 polyA signal is a standard signal for termination of transcripts (e.g., EXAMPLE IX).

From the confluence of this, it is clear that Jolly teaches transfection of macrophages *in vivo* with plasmids, Hedley and Samlowski teaches that transformation of the macrophages will lead to transfected cells in the draining lymph nodes, and Kataoka and Bonadio teach the required signals for expression of a gene in macrophages.

Further, when injecting substances, it is standard in the Art to administer substances which numb the area to avoid hurting the subject. One such substance which is well known in the Art is Bupivacaine (http://www.drugdigest.org/DD/DVH/Uses/0,3915,7903%7CBupivacaine%2BHCL,00.html). Hence, the further administration of Bupivacaine was well known in the Art for such use, and as such the further utilization of Bupivacaine would be obvious.

Therefore, at the time of invention, the method would have been obvious. The Artisan would choose a site local to the lymph node target, which will be intramuscular, depending on which lymph nodes are being targeted (it is well known in the Art that lymph nodes are located throughout the body and near muscle) because the macrophages were known to drain to local lymph nodes. Still further, the Artisan would inject the plasmid by IM injection in order to deliver it to a lymph node local to the muscle injection site. Still further, the administration of

Bupivacaine to a subject during or prior to injection of the vector would be motivated in order to avoid pain in the subject due to administration. Moreover, the Artisan would have expected success, as the transformation of macrophages was already well known and the draining of such macrophages to lymph nodes was well known in the Art. In addition, the obtained result would necessarily be obtained as the macrophage is secreting the protein.

Arguments of specific motivation are now precluded by KSR v. Teleflex. In essence, Applicant's claims reflect what is already known in the Art to occur and is simply another method that the Artisan would be capable of performing prior to the invention in order to get proteins into the lymph nodes. In addition, without a requirement of the amounts of protein or some other limitation such that the Artisan would not expect it to work, there is a reasonable expectation of success.

For purposes of speeding an anticipated appeal, the following explanation is provided. The methods of the invention center around the administration of a vector to a tissue in order to transform and express a protein from macrophages, which protein is then secreted by the macrophage. The macrophage subsequently drains into a local lymph node, thereby providing the protein to the lymph node in the form of its secretion from the macrophage. The Art demonstrates that the methods of transforming macrophages, the use of promoters specific for macrophages to effect their tissue-specific expression in macrophages, the use of secretion signals, and the use of the polyA tails was well known in the Art. Still further, and critically, the Art recognized that macrophages drained into lymph nodes local to their tissue site, as shown in Samlowski. The question then, appears to the Examiner to be whether or not the Artisan would have been able to put together these functions and utilize them derive a method encompassed by

the claims. The Examiner maintains that this knowledge is within the skill of the Artisan, and the non-specific motivation is the combined knowledge in the Art that the macrophages drain to local lymph nodes, with the known mechanisms of causing the macrophages to secrete a protein.

Response to Argument – obviousness

Applicant's argument of 10/14/08 has been fully considered but is not found persuasive.

Applicant argues that Jolly does not disclose how to administer the vector to a macrophage (p. 7, paragraph 3).

Such is not persuasive. Jolly teaches that naked plasmids may be used to transfect macrophages (e.g., paragraph 0037). Moreover, as Applicant must know, macrophages are known in the art for taking up nucleic acids that are local to them. For example, Takagi, et al. (1998) Biochemical and Biophysical Research Communications, 245: 729-733, e.g., ABSTRACT, indicates that it is was known that macrophages incorporate plasmid DNA taken up by scavenging the region local to the macrophage. Hence, the Artisan clearly already knew that macrophages took up plasmids in their environment. Moreover, it is not Jolly that is required to teach the aspect of delivery of vectors to macrophages, but the Art cited must make it obvious.

Applicant argues that Jolly does not disclose identifying a site proximal to a lymph node and delivery to the lymph node by macrophage draining (p. 7, paragraph 3).

Such is not persuasive. The Art cited is not required to teach the specific limitation, but simply to make obvious the limitations. Such has been sufficiently addressed.

Applicant argues that Hedley teaches away from the use of free DNA and IM administration, by discussing microparticles that are effective for deliverying DNA to be taken up the macrophages (p. 7, paragraph 4).

Headley's specific microparticles are not teaching away from the use of free DNA, as it does not disparage the use of such. Headley's particles, whether or not free DNA do not take away the fact that plasmid DNA is similarly taken up by macrophages. Additional teachings do not take away from that already known in the Art to work, e.g., as shown in the art cited and in Takagi, as cited in the Arguments above.

Applicant argues that Headley teaches away from IM injection, as it teaches targeting via subcutaneous injection, to target local lymph nodes (p. 7, last paragraph).

Such is not persuasive. Headley, as recognized in the rejection, teaches subcutaneous injection, however, Headley is not used to teach IM injection, but simply to demonstrate the known aspect of targeting local lymph nodes. Applicant is requested to reread the rejection. Hence, references to intramuscular injection in Headley are not even relevant to what Headley is used for.

Applicant argues that Headley teaches away from using free DNA (p. 8, paragraph 1).

Such is not persuasive. Headley's use of microparticles does nothing to disparage the use of naked DNA. There is nothing in Headley to indicate to the Artisan that free DNA would not be taken up by the macrophages.

Applicant argues that the Artisan would not combine Headley with the other references, as they do not make up for the deficiencies.

Such is not persuasive. It is clear that there are no deficiencies still missing to be overcome. Moreover, the Examiner sees no reason that the Artisan would avoid combining the references, as there is nothing that would be considered inoperative after combining the information which is combined.

Applicant argues unexpected results, arguing that the Artisan would not expect intramuscular injection to deliver the protein to a lymph node, or expect that free DNA could be used to deliver DNA (p. 8, paragraphs 3-4).

Such is not persuasive. Jolly teaches naked DNA use. Moreover, Tagaki teaches that macrophages of the liver were already known to uptake naked DNA, and further demonstates that peritoneal macrophages will do the same, even suggesting a mechanism (p. 729, whole page). Hence, it would appear that the Artisan fully understood that macrophages took up naked DNA. Moreover, as the references show that macrophages drain to local lymph nodes, it how could it be that once transformed, they would not go to these lymph nodes? The Examiner simply sees no nexus to disbelieve that it would work, such that the claims would be allowable.

Applicant argues that it is surprising that the DNA is not degraded in the process performed (p. 8, paragraph 5).

Such is not persuasive. First, what is surprising to Applicant is not necessarily what is surprising to the Artisan. Second, there is no evidence that some of the DNA is not degraded. Third, as shown in the art in the Argument, Takagi demonstrates that it was known that genes in such DNA are uptaken by macrophages, as taught by Jolly. The Examiner fails to find persuasive here as to why it is unexpected, much less what is unexpected.

Applicant argues that prior to their disclosure it was not known or obvious to deliver a protein to a lymph node via the methods claimed (p. 9, paragraph 2).

Such is not persuasive. While it is admitted that it was not known to do to, as is evidenced by the absence of a rejection under 35 USC 102, it was obvious, for the reasons given. The simple known methods and consequences in the Art allowed the Artisan to use such mechanisms to obtain the same results. There is simply nothing not obvious about the method and consequences. Applicant's contribution appears to the Examiner to be the specific motivation to do so, because they put together the known methods in the Art, however, motivation, as elucidated in KSR v. Teleflex, is not required to be specific.

Applicant argues that the Examiner has failed to articulate the rejection with reasoning to underpin the legal conclusion of obviousness, and specifically the Office only provides that macrophages will uptake DNA upon subcutaneous injection (p. 9, paragraph 3).

Such is not persuasive. The rejection is proper, as Jolly teaches that macrophages will take up such particles, including free DNA. Moreover, such is supported by the knowledge of the Artisan, which is the standard by which obvious is given. For example, Takagi demonstrates that the Artisan knew that macrophages of any tissue took up naked DNA (argued above). Hence, the rejection is proper. There is simply nothing not sufficiently articulated such that the Artisan would not understand the rejection.

The rejections are maintained, as necessitated by amendment.

CONCLUSION

No Claim is allowed.

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to ROBERT M. KELLY whose telephone number is (571)272-0729. The examiner can normally be reached on M-F, 9:00am-5:00pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Joseph Woitach can be reached on (571) 272-0739. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Robert M Kelly/
Primary Examiner of Art Unit 1633